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To evaluate the effect of a phytoestrogen supplement on steroid hormones and their target tissues, 60 disease-free postmenopausal breast cancer survivors are being randomized to either 100mg/d isoflavone tablets or placebo for one year. Hormone levels are measured at baseline, 6 months, and one year. Changes in menopausal symptoms, vaginal maturation, and breast epithelial proliferation are also being measured.

The trial was opened to accrual in June 2001. As of June 2002, 631 breast cancer patients had been screened through the Seattle Cancer Care Alliance. We received 56 additional self or clinician referrals. From both groups, 467 were found to be ineligible, 52 refused participation. The number one reason for ineligibility at our institution is stage (75%). Of the eight women who stated their primary reason for refusal, the most common reasons have been complaints of invasiveness of the trial (15%) and unwillingness to take phytoestrogen supplements (31%).

In order to increase recruitment yield, a mechanism to see patients who receive their oncologic care outside the sponsoring institution was developed, and a community outreach campaign begun. In the past month, 4 more women have been randomized. We expect to have full data on 8 subjects and mid-intervention data on at least 6 subjects by the time of the next annual report.

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Table of Contents

Modulation of Postmenopausal Steroid Hormone Levels by Phytoestrogens and Correlation with Breast Proliferative Activity and Menopausal Symptoms

Melanie R. Palomares, MD and Julie R. Gralow, MD

Introduction:

Overall 5-year survival from breast cancer is now 85%, and most surviving women are postmenopausal. Nearly half of postmenopausal American women take estrogen replacement to relieve hot flashes and other symptoms of menopause, but this is contraindicated in women with breast cancer. Phytoestrogen supplements can be used as an alternative, but their effect on the risk of cancer recurrence is unknown. Given the mixed results of phytoestrogen studies regarding breast cell stimulation and inhibition in the medical literature, the effect of phytoestrogens on postmenopausal breast cancer survivors is unclear. To evaluate the effect of a phytoestrogen supplement on steroid hormones and breast epithlial proliferation, 60 disease-free, post-therapy, postmenopausal women with in-situ or early invasive (St. 0-II) breast cancer are being randomized to either 100mg/d isoflavone tablets or placebo for one year. Hormone levels are measured at baseline, 6 months, and one year. Changes in menopausal symptoms and vaginal maturation are also being measured.

Body:

Task 1: Study Preparation - completed

a. Development of materials – completed

Brochures, flyers, advertisements, web pages, cover letters, as well as data collection forms and study charts were developed. Screening and study data databases were designed and tested for use as well. Both active and placebo tablets were obtained.

b. Mailings to patients, clinicians, support groups – completed

Patients receiving their oncologic care at the Seattle Cancer Care Alliance, and their support groups and care providers were mailed informational materials just prior to when the trial opened to accrual in June 2001. Since then, patients have been approached for recruitment at the time they come in for their clinical follow-up.

Task 2: Subject Recruitment - ongoing

As of June 2002, 631 breast cancer patients had been screened through the Seattle Cancer Care Alliance. We received 56 additional self or clinician referrals. From both groups, 467 were found to be ineligible, 52 refused participation. The number one reason for ineligibility at our institution is stage (75%). Of the eight women who stated their primary reason for refusal, the most common reasons have been complaints of invasiveness of the trial (15%) and unwillingness to take phytoestrogen supplements (31%). Surprisingly, refusal to take isoflavone tablets has been more of a deterrent to participation than the breast biopsy so far. This has been due to a fear of stimulation of recurrence, as well as an unwillingness to be randomized to active vs. placebo tablets

because of either strong desire for active tablet (unacceptance of placebo control) or preference for a dietary intervention.

At the first meeting of the Data Safety Monitoring Committee in December 2001, it was determined that we were behind accrual goals. In order to increase recruitment yield, the investigators have agreed to relax the stage eligibility criteria to include women with Stage IIB breast cancer, as long as fewer than 4 lymph nodes were involved. A mechanism to see patients who receive their oncologic care outside the sponsoring institution was also subsequently developed, and a community outreach campaign begun. In the past month, 4 more women have been randomized.

In a formal analysis comparing of clinic and community based recruitment in the first year of the trial, we found that community based recruitment has yielded more participants. Specifically, 41 eligible women were identified through the clinic over 12 months. However, 80% of those who are currently eligible refused participation. On the other hand, community based recruitment has yielded 25 eligible women over 6 months, and those who were eligible were 15 times more likely to participate. This analysis was presented at the American Institute for Cancer Research meeting in June (see Reportable Outcomes section).

Task 3: Clinical Trial - ongoing

Of the 14 subjects randomized, none have reported side effects attributable to the isoflavone tablets. One woman developed a small post biopsy hematoma, and 2 complained of the dressings used, but the others have not complained of significant discomfort with their breast biopsies. Blood collections for serum hormone evaluations at baseline, 6 months, and one year are ongoing. Serum is aliquotted and frozen at –70C within 8 hours of blood collection.

Task 4: Study Follow-up – scheduled to begin next year

Of the 14 randomized subjects, two have entered this phase of the study so far.

Task 5: Evaluation of Clinical Materials – scheduled to begin next year

Of the 14 randomized subjects, we expect to have full data on 8 subjects and mid-intervention data on the remaining 6 by the time of the next annual report. With the addition of community based recruitment, we expect to have 60 subjects randomized by June 2003.

Task 6: Data Analysis and Report Writing – scheduled for year #3

Key Research Accomplishments:

- Conduct of a breast chemoprevention trial with histologic endpoints requiring breast biopsy appears feasible.

- Community-based recruitment is proving more effective than clinic-based recruitment

- Isoflavone tablets and breast biopsies are well tolerated by participating subjects thus far.

Reportable Outcomes:

Palomares MR and Gralow JR. "The Effect of Phytoestrogens on Normal Breast Tissue in Postmenopausal Breast Cancer Surivors: An Ongoing Trial," Proceedings of the AICR / WCRF International Research Conference on Food, Nutrition and Cancer, 2002.

Conclusions:

We await years #2 and 3 of the study to address the proposal's specific aim of determining if changes in estrogen, androges, and sex hormone binding globuljn levels after 6 and 12 months of isoflavone intervention are significantly different from placebo.

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THE EFFECT OF PHYTOESTROGENS ON NORMAL BREAST TISSUE IN POSTMENOPAUSAL BREAST CANCER SURVIVORS

Melanie R. Palomares, MD and Julie R. Gralow, MD

Phytoestrogens have received media attention as a form of breast cancer prevention. Although epidemiologic studies support this claim, there are no prospective clinical trials demonstrating such a protective effect. This project, supported by an AICR Postdoctoral Award, aims to evaluate the effect of a phytoestrogen supplement on the breast tissue of postmenopausal breast cancer survivors. Sixty disease-free, post-therapy, postmenopausal women with in-situ or early invasive (St. 0-II) breast cancer are to be randomized to either 100mg/d isoflavone tablets or placebo for one year. Biopsies of the uninvolved breast are examined for proliferative changes in response to phytoestrogens, as well as immunohistochemical breast cancer biomarkers. Mammography is performed to assess breast density, and for close monitoring for recurrence. As secondary endpoints, menopausal symptoms, vaginal epithelial changes, endometrial histology, and serum steroid hormones are also being measured.

The trial was opened to accrual in June 2001. Since then, 631 breast cancer patients have been screened through the Seattle Cancer Care Alliance. We received 56 additional self or clinician referrals. From both groups, 467 were found to be ineligible, 52 refused participation, and 14 have consented to participate so far. The number one reason for ineligibility at our institution is stage (75%). Of the eight women who stated their primary reason for refusal, the most common reasons have been complaints of invasiveness of the trial (15%) and unwillingness to take phytoestrogen supplements (31%). Of the 10 women actually enrolled in the study, none have reported side effects attributable to the isoflavone tablets. One woman developed a small post biopsy hematoma, and 2 complained of the dressings used, but the others have not complained of significant discomfort with their breast biopsies.

In order to increase recruitment yield, a mechanism to see patients who receive their oncologic care outside the sponsoring institution has been developed, and a community outreach and education campaign regarding phytoestrogens begun. Mammographic density will be followed to see if it can serve as a noninvasive endpoint for breast epithelial proliferation.